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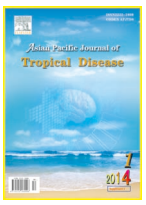

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The importance of eosinophil, platelet and dendritic cell in asthma

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PEER REVIEW

Peer reviewer

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Comments

This is a good study in which the authors stated the importance of eosinophil, platelet, and DC in asthma and future of treatment. The data are interesting. The results can be used in the treatment and control of asthma.
Details on Page S44

ABSTRACT

Asthma is a syndrome of variable airflow obstruction. It is characterized pathologically by bronchial inflammation and remodeling changes. Eosinophil infiltrate in asthma and a relationship between the degree of eosinophil infiltration in airways and severity of asthma has been suggested. Eosinophil has antigen-presenting cells and main role in allergic asthma. Platelets in inflammatory response is very important. It has also been shown that enzymes released by activated platelets play a direct role in the chronic inflammatory events that lead to airway remodeling in asthma. Dendritic cells (DCs) acquire antigen in the airways and then migrate to the draining lymph node where the cells mature and initiate T cell responses. Allergen challenge induces simultaneous increases in the number of DCs in the lungs. Because DCs are crucial in mounting immune responses during ongoing inflammation in the lung and balance of the allergic immune response.

KEYWORDS
Allergic asthma, Eosinophil, Platelet, Dendritic cell

1. Introduction

Asthma is a chronic respiratory problem characterized by recurring attacks of impaired breathing, of varying intensities. The definition of asthma has four cardinal components which are bronchoconstriction, symptoms, airway inflammation, and airway hyper-responsiveness. Few new drugs representing novel modes of action have been introduced over the last 30 years[1-3]. Indeed the mainstays of treatment, in the form of inhaled corticosteroids, b2 adrenoceptor agonists and cholinergic antagonists, were first used clinically[4,5]. None of these drugs prevent asthma. The goal of therapy is two-fold to limit the current impairment or symptoms, and to reduce the risk for a severe attack in the future. Since even patients with mild asthma have evidence for inflammation of the large and small airways, and the severity of the inflammation often correlates with the severity of the disease[6-8]. The cellular pathology, recognition receptors, co-stimulatory molecules, key transcription factors, cytokines, chemokines, adhesion molecules, and other mediators, have been investigated and incorporated into a comprehensive, detailed, unifying model of the events that translate into asthma[9-11].

2. Mechanisms of asthma

Asthma is a syndrome of variable airflow obstruction. It is

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characterized pathologically by bronchial inflammation and remodeling changes, physiologically by bronchial hyper-responsiveness, and clinically by cough, chest tightness and wheeze. Cytokines secreted by CD4+Th2 type T cells play a major role in allergic asthma and other effectors cells, such as myofibroblasts, epithelial cells, smooth muscle cells and endothelial cells, which play an intermediary role in airways damage and remodeling[12-15]. Etiological trigger factor for asthma is exposure to environmental antigens, in particular inhaled allergens, including occupational allergens and infectious agents, which are probably a major drive to T cell activation in asthma. Genetic factors governing the production of T cell cytokines and their actions on target cells, as well as variability in the structure and development of the mesenchymal elements of the bronchial mucosa influence the risk of developing asthma[16-18].

3. Eosinophil function in asthma

Eosinophils are suspected in the inflammatory infiltrate in asthma and a relationship between the degree of eosinophil infiltration in airways and severity of asthma has been suggested. The severity of asthma correlates with levels of circulating and bone marrow eosinophils, and the evaluation of asthma has usually involved determination of eosinophil counts[19-21]. Eosinophil-derived cationic proteins are also detectable in plasma of asthma patients. Eosinophils, through their release of basic proteins and lipid mediators, are strongly implicated in mucosal damage and involved in mechanisms that underlie bronchial hyperreactivity. When asthma is under remission due to corticosteroid therapy, levels of circulating eosinophils plummet[19-22]. Asthma patients develop a low density population of circulating eosinophils. Large numbers of eosinophils are recoverable from sputum and bronchoalveolar lavage of asthma patients, and the levels of eosinophils correlate with the severity of asthma. Circulating IL-5 is often detectable in asthma patients[23-25]. The histopathology of asthma shows massive infiltration of the bronchial mucosa by eosinophils and other inflammatory cells and an associated deposition of eosinophil granule cationic proteins. This is associated with structural changes that include damage to or loss of ciliated epithelial cells, thickening of the basement membrane, and the accumulation of mucus and debris[26,27].

Bronchial associated eosinophils have physical and functional characteristics that demonstrate a state of activation, which include reducing density and elevating protein kinase C activity. There are several direct mechanisms by which eosinophils may cause disease. The toxicity of eosinophil cationic proteins and oxygen metabolites may be responsible for the damage to ciliated cells and the desquamation of the tracheal epithelium that is observed with the disease. Major basic protein (MBP) induces airway smooth muscle constriction and hyperresponsivenessin. Pulmonary parasympathetic nerves release acetylcholine, which binds smooth muscle M3 muscarinic receptors and stimulates bronchoconstriction. Acetylcholine release is self-regulatory by a mechanism that involves binding to M2 muscarinic receptors on the nerve endings. It was found that MBP inhibits the binding of the drug N-methylscopolamine to M2 but not M3 receptors. This shows that MBP alters the binding properties of the inhibitory M2 receptor and have the potential to block the feedback suppression of acetylcholine release[28-30].

The eosinophil has the greatest capacity for leukotriene C4 (LTC4) synthesis of any cell associated with inflammation. LTC4 can induce smooth muscle constriction and microvascular permeability. This substance is thought to contribute to the stromal fibrosis and basement membrane thickening that is observed in this asthma. This mechanism may also produce similar changes in asthma. In addition to these direct mechanisms for the induction of hyperresponsiveness and bronchoconstriction, eosinophils have the potential to make indirect contributions by the production of mediators that stimulate the functions of other inflammatory cells[31-34].

4. Eosinophilic airway inflammation in bronchial asthma

Eosinophils preferentially accumulate at sites of allergic inflammation and are believed to play important roles in the pathophysiology of asthma through the release of a variety of inflammatory mediators, including MBP, cysteinyl leukotrienes (CysLTs), radical oxygen species, and cytokines[35-37]. In asthmatic patients with persistent sputum eosinophilia, treatment with anti-IL-5 mAb reduced asthma exacerbations and the requirement for systemic corticosteroids, and improved asthma-related quality of life. These results strongly suggest essential role of eosinophils in the development of asthma exacerbation. Furthermore, antagonizing IL-5 could be an effective strategy for controlling refractory eosinophilic asthma as well as controlling hypereosinophilic syndrome[5,38-40]. Eosinophils largely contribute to the development of airway remodeling of asthma. During the season for pollen allergy, however, only eosinophils, but not mast cells or macrophages, express LTC4 synthase in the bronchial tissue. So eosinophils are a major cellular source of CysLTs in asthma. For circulating eosinophils to accumulate in asthmatic airways, they must adhere to and then migrate across vascular endothelial cells. These processes are largely regulated by cytokines/chemokines produced by a variety of cells, including Th2 cells[41,42]. Accumulating evidence has suggested that

eosinophil interaction with endothelial cells via the integrin/vascular cell adhesion molecule (VCAM)-1 pathway is likely a key step for selective eosinophil recruitment. Th2 cytokines IL-4 and IL-13 have potent activity for endothelial cells to express VCAM-1, and blood eosinophils spontaneously adhere to VCAM-1. The interaction of eosinophils and VCAM-1 results in the respiratory burst and enhancement of granule protein release from eosinophils. CC chemokines, including regulated upon activation normal T cell expressed and secreted, eotaxin, eotaxin-2, monocyte chemotactic protein-3, and monocyte chemotactic protein-4, selectively augment eosinophil transmigration across endothelial cells expressing VCAM-1[43-45]. The cellular sources of CC chemokines are likely to be epithelial cells, fibroblasts, and mononuclear cells. Therefore, CC chemokines are increased in the airways of asthma. Following migration across endothelial cells, eosinophils can be effectively activated and degranulated by granulocyte-macrophage colony-stimulating factor, even in the absence of IL-5[46-48].

5. Eosinophils function as professional antigen-presenting cells (APCs)

Several studies demonstrating the trafficking of eosinophils to lymph nodes suggest, not only do eosinophils express MHC class II and co-stimulatory molecules, they function as APCs. Human eosinophils can process and present ovalbumin, bee venom, parasitic antigens and tetanus toxoid to antigen-specific T cells in co-culture, causing their proliferation. So eosinophils are actively processing antigen[49-52]. There is now a substantial body of evidence that demonstrates that eosinophils have the ability to stimulate naive T cells. Several prior studies reported that murine eosinophils did not have the ability to prime naive T cells, a defining criterion for professional APCs and only had the ability to stimulate previously primed T cells. Furthermore, several new researches show that the ability of eosinophils to stimulate naive T cells in this experimental system was actually equivalent to that of dendritic cells. MHC class II in human eosinophils localizes to lipid rafts domains that mediate spatial organization of membrane proteins. Lipid raft integrity is essential to stimulation of T cells by eosinophils in a superantigen-mediated fashion[53-56].

6. Platelets

The airway inflammation seen in allergic asthma is associated with recruitment and activation of inflammatory cells. Recent researches have shown that activated platelets play a critical role in the development of inflammation in allergic asthma. In allergic asthma, allergen exposure induces platelet activation and migration to the airways where they activate leukocytes. Activated leukocytes show an increase in expression of cluster of differentiation molecule 11B and very late antigen-4, adhesion molecules that are necessary for inflammatory cell attachment to the airway vascular endothelium[57-60]. Additionally, it has also been shown that platelets play a critical role in airway remodeling as a result of chronic allergen exposure. It is well established that allergic asthma is associated with inflammation and airway epithelial damage. Specifically, following an allergic stimulus, inflammatory cell activation and migration to asthmatic airways so the role of platelets in inflammatory response is very important. It has also been shown that enzymes released by activated platelets play a direct role in the chronic inflammatory events that lead to airway remodeling in asthma[61-64].

7. Association of dendritic cells (DCs) subpopulations with inflammation

DCs are known to play a central role in sensing the presence of foreign antigens and infectious agents and in initiating appropriate immune responses[65,66]. Allergic asthma increases the sputum numbers of both inflammationassociated myeloid DCs and tolerance-associated plasmacytoid DCs. Allergen challenging induced a selective decrease in airway myeloid DCs, with no decrease in plasmacytoid DC numbers[67,68].

8. DCs in the lungs, asthma, and allergy

Lung myeloid DCs have been shown to be critical in mediating allergic responses to inhaled antigens. In normal conditions, airway and lung DCs are immature and are more likely to induce Th2. DCs acquire antigen in the airways and then migrate to the draining lymph node where the cells mature and initiate T cell responses. Allergen challenge induces simultaneous increases in the number of DCs in the lungs and in the lymph nodes, as well as increases in the number of DC precursors in the bone marrow[69-72]. One of the important aspects of the function of the lung's immune system is that hematopoietic cells can migrate bidirectionally, from the tissues into the airspace as well as from the airspace's back into the lung tissue and the draining lymph nodes. The site of DC transmigration from the airspace into the lung tissue is not clear[73-75].

9. DCs as drug targets in allergic diseases

Because DCs are crucial in mounting immune responses

during ongoing inflammation in the lung, so interfering with their function could constitute a novel form of treatment for allergic diseases. Additionally, pharmacological modification of DCs might fundamentally reset the balance of the allergic immune response in favor of regulatory T cells and thus lead to a more longlasting effect on the natural course of allergic disease. Inhaled steroids reduce the number of lung DCs in patients with allergic asthma[76-80].

10. DC targeting to treat allergic disease

Several unique molecules have been identified that may alter DC function in allergic inflammation and therefore could be possible therapeutic targets. Many of these compounds were first discovered by their potential to interfere with DC-driven Th2 cell sensitization[81-84]. So studying the factors that control recruitment, survival, or egress of DCs from the lung during allergic inflammation will be important, because this might reveal new therapeutic targets. More detailed information on the interactions between DCs, epithelial cells, basophils, and other inflammatory cells will undoubtedly lead to the discovery of more potentially interesting drugs[69,85-88].

11. Discussion

Airway inflammation is an important feature of asthma and occurs simultaneously with increased bronchial hyperreactivity. The eosinophil has the greatest capacity for LTC4 synthesis of any cell associated with inflammation. Eosinophils can be effectively activated and degranulated and do allergic reaction in lung. Therefore eosinophils have function as professional APCs[89-93]. Activated platelets have been shown to be increased in asthmatic airways. Additionally, it has been demonstrated that in the presence of platelets derived from patients with asthma, eosinophil attachment to airway endothelium is enhanced[94,95]. Therapeutic strategies try targeting DCs to change immune responses to allergens from allergic to tolerogenic promise to provide a long-term cure of allergies and asthma. Therapeutic strategies aimed specifically at DCs to treat allergies and asthma are being developed. These strategies could include vaccination with allergen-loaded, tolerogenic DCs made *in vitro* or targeting of antigen to tolerogenic DCs *in vivo*. So many clinical trials have shown that DC-based vaccines are safe and can be effective[96-100]. Therefore, asthma is a very complicated problem that many molecules and cells have role and each cell is important and notable for control and treatment of allergic asthma. This view shows that DC, eosinophil and platelet have key role in allergic asthma and interaction between cells that is very important.

Conflict of interest statement

We declare that we have no conflict of interest.

Comments

Background

Asthma is a chronic respiratory problem that is characterized pathologically by bronchial inflammation and remodeling changes. Some cells have main role in pathogenesis of asthma that was reviewed in this manuscript.

Research frontiers

This review states that eosinophil, platelet and DC are very important in asthma, which is a chronic inflammatory disease of the airway.

Related reports

As this is a review study, therefore it is done with others study and others research background. Humbles *et al.* reported an important role of eosinophils in allergic airways remodeling. Akuthota *et al.* studied eosinophils as antigen-presenting cells in allergic upper airway disease.

Innovations & breakthroughs

This study has showed that harness main cells of allergic asthma (eosinophil, platelet, and DC) had an important role to control of asthma.

Applications

The results of the present study suggest that with drugs that have effect in mentioned cells, asthma could be controlled and treatment. So attention to these cells is important.

Peer review

This is a good study in which the authors stated the importance of eosinophil, platelet, and DC in asthma and future of treatment. The data are interesting. The results can be used in the treatment and control of asthma.

References

[1] Kevin M. Asthma translational medicine: report card. *Biochem Pharmacol* 2011; **82**: 567-585.

[2] Wills-Karp M, Ewart SL. The genetics of allergen-induced airway hyperresponsiveness in mice. *Am J Respir Crit Care Med* 1997; **156**: 89-96.

[3] Li XM, Schofield BH, Wang QF, Kim KH, Huang SK. Induction of pulmonary allergic responses by antigen-specific Th2 cells. *J Immunol* 1998; **160**: 1378-1384.

[4] Van Rijt LS, Jung S, Kleinjan A, Vos N, Willart M, Duez C, et al. *In vivo* depletion of lung CD11c+ dendritic cells during allergen challenge abrogates the characteristic features of asthma. *J Exp Med* 2005; **201**: 981-991.

[5] Lee JJ, Dimina D, Macias MP, Ochkur SI, McGarry MP, O'Neill KR, et al. Defining a link with asthma in mice congenitally deficient in eosinophils. *Science* 2004; **305**: 1773-1776.

[6] Elias J. The relationship between asthma and COPD. Lessons from transgenic mice [discussion]. *Chest* 2004; **126**(Suppl 2): S159-S161.

[7] Finotto S, Neurath MF, Glickman JN, Qin S, Lehr HA, Green FH, et al. Development of spontaneous airway changes consistent with human asthma in mice lacking T-bet. *Science* 2002; **295**: 336-338.

[8] Barnes PJ. The cytokine network in asthma and chronic obstructive pulmonary disease. *J Clin Invest* 2008; **118**: 3546-3556.

[9] Palmqvist C, Wardlaw AJ, Bradding P. Chemokines and their receptors as potential targets for the treatment of asthma. *Br J Pharmacol* 2007; **151**: 725-736.

[10] Ying S, O'Connor B, Ratoff J, Meng Q, Mallett K, Cousins D, et al. Thymic stromal lymphopoietin expression is increased in asthmatic airways and correlates with expression of Th2-attracting chemokines and disease severity. *J Immunol* 2005; **174**: 8183-8190.

[11] Lombardi V, Singh AK, Akbari O. The role of costimulatory molecules in allergic disease and asthma. *Int Arch Allergy Immunol* 2010; **151**: 179-189.

[12] Lemanske RF, Busse WW. Asthma: clinical expression and molecular mechanisms. *J Allergy Clin Immunol* 2010; **125**(Suppl 2): S95-S102.

[13] James AL, Wenzel S. Clinical relevance of airway remodelling in airway diseases. *Eur Respir J* 2007; **30**: 134-155.

[14] Kraft M. Asthma phenotypes and interleukin-13: moving closer to personalised medicine. *New Engl J Med* 2011; **365**: 1141-1144.

[15] Corrigan CJ, Wang W, Meng Q, Fang C, Wu H, Reay V, et al. T-helper cell type 2 (Th2) memory T cell-potentiating cytokine IL-25 has the potential to promote angiogenesis in asthma. *Proc Natl Acad Sci USA* 2011; **108**: 1579-1584.

[16] Holgate ST, Holloway J, Wilson S, Bucchieri F, Puddicombe S, Davies DE. Epithelial-mesenchymal communication in the pathogenesis of chronic asthma. *Proc Am Thorac Soc* 2004; **1**: 93-98.

[17] Mahn K, Hirst SJ, Ying S, Holt MR, Lavender P, Ojo OO, et al. Diminished sarco/endoplasmic reticulum Ca2+ATPase (SERCA) expression contributes to airway remodelling in bronchial asthma. *Proc Natl Acad Sci USA* 2009; **106**: 10775-10780.

[18] Grainge CL, Lau LC, Ward JA, Dulay V, Lahiff G, Wilson S, et al. Effect of bronchoconstriction on airway remodelling in asthma. *N Engl J Med* 2011; **364**: 2006-2015.

[19] Krause JR, Boggs DR. Search for eosinopenia in hospitalized patients with normal blood leukocyte concentration. *Am J Hematol* 1987; **24**: 55-63.

[20] Horn BR, Robin ED, Theodore J, Van Kessel A. Total eosinophii counts in the management of bronchial asthma. *N Engl J Med* 1975; **292**: 1152-1155.

[21] Filley WV, Holley KE, Kephart GM, Gleich GJ. Identification by immunofluorescence of eosinophil granule major basic protein in lung tissue of patients with bronchial asthma. *Lancet* 1982; **2**: 11-16.

[22] Fukuda T, Dunnette SL, Reed CE, Ackerman SJ, Petetrs MS, Gleich GJ. Increased numbers of hypodense eosinophils in the blood of patients with bronchial asthma. *Am Rev Respir Dis* 1985; **132**: 981-985.

[23] Durham SR, Kay AB. Eosinophils, bronchial hyperreactivity and late-phase asthmatic reactions. *Clin Allergy* 1985; **15**: 411-418.

[24] Dahl R, Venge P, Olsson I. Variations of blood eosinophils and eosinophil cationic protein in serum in patients with bronchial asthma: studies during inhalation challenge test. *Allergy* 1978; **33**: 211-215.

[25] Juntunen-Backman K, Järvinen P, Sorva R. Serum eosinophil cationic protein during treatment of asthma in children. *J Allergy Clin Immunol* 1993; **92**: 34-38.

[26] Shult PA, Lega M, Jadidi S, Vrtis R, Warner T, Graziano FM, et al. The presence of hypodense eosinophils and diminished chemilumunescence response in asthma. *J Allergy Clin Immunol* 1988; **81**: 429-437.

[27] Calhoun WJ, Bates ME, Schrader L, Sedgwick JB, Busse WW. Characteristics of peripheral blood eosinophils in patients with nocturnal asthma. *Am Rev Respir Dis* 1992; **145**: 577-581.

[28] Warringa RA, Mengelers HJ, Raaijmakers JA, Bruijnzeel PL, Koenderman L. Upregulation of formyl-peptide and interleukin-8-induced eosinophil chemotaxis in patients with allergic asthma. *J Allergy Clin Immunol* 1993; **91**: 1198-1205.

[29] Bradley BL, Azzawi M, Jacobson M, Assoufi B, Collins JV, Irani AM, et al. Eosinophils, T-lymphocytes, mast cells, neutrophils, and macrophages in bronchial biopsy specimens from atopic subjects with asthma: comparison with biopsy specimens from atopic subjects without asthma and normal control subjects and relationship to bronchial hyper-responsiveness. *J Allergy Clin Immunol* 1991; **88**: 661-674.

[30] Talley NJ, Kephart GM, McGovern TW, Carpenter HA, Gleich GJ. Deposition of eosinophil granule major basic protein in eosinophilic gastroenteritis and coehac disease. *Gastroenterology* 1992; **103**: 137-145.

[31] Laitinen LA, Heino M, Laitinen A, Kava T, Haahtela T. Damage of the airway epithelium and bronchial reactivity in patients with asthma. *Am Rev Respir Dis* 1985; **131**: 599-606.

[32] Wardlaw AJ, Dunnette S, Gleich GJ, Collins JV, Kay AB. Eosinophils and mast cells in bronchoalveolar lavage in subjects with mild asthma: relationship to bronchial hyperreactivity. *Am Rev Respir Dis* 1988; **137**: 62-69.

[33] De Monchy JG, Kauffman HF, Venge P, Koëter GH, Jansen HM, Sluiter HJ, et al. Bronchoalveolar eosinophilia during allergen-induced late asthmatic reactions. *Am Rev Respir Dis* 1985; **131**: 373-376.

[34] Gundel RH, Gerritsen ME, Gleich GJ, Wegner CD. Repeated antigen inhalation results in prolonged airway eosinophiha and airway hyperresponsiveness in primates. *J Appl Physiol* 1990; **68**: 779-786.

[35] Gleich GJ. Mechanisms of eosinophil-associated inflammation. *J Allergy Clin Immunol* 2000; **105**: 651-663.

[36] Weller PF. Human eosinophils. *J Allergy Clin Immunol* 2000; **100**: 283-7.

[37] Flood-Page PT, Menzies-Gow AN, Kay AB, Robinson DS. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway. *Am J Respir Crit Care Med* 2003; **167**: 199-204.

[38] Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009; **360**: 985-993.

[39] Humbles AA, Lloyd CM, McMillan SJ, Friend DS, Xanthou G, McKenna EE, et al. A critical role for eosinophils in allergic airways remodeling. *Science* 2004; **305**: 1776-1779.

[40] Bochner BS. Cellular adhesion its antagonism. *J Allergy Clin Immunol* 1997; **100**: 581-585.

[41] Schleimer RP, Sterbinsky SA, Kaiser J, Bickel CA, Klunk DA, Tomioka K, et al. IL-4 induces adherence of human eosinophils and basophils but not neutrophils to endothelium. Association with expression of VCAM-1. *J Immunol* 1992; **148**: 1086-1092.

[42] Nagata M, Sedgwick JB, Vrtis R, Busse WW. Endothelial cells upregulate eosinophil superoxide generation via VCAM-1 expression. *Clin Exp Allergy* 1999; **29**: 550-561.

[43] Sabatini F, Silvestri M, Sale R, Scarso L, Defilippi AC, Risso FM, et al. Fibroblast-eosinophil interaction: modulation of adhesion molecules expression and chemokine release by human fetal lung fibroblasts in response to IL-4 and TNF-alpha. *Immunol Lett* 2002; **84**: 173-178.

[44] Leckie MJ, ten Brinke A, Khan J, Diamant Z, O'Connor BJ, Walls CM, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet* 2000; **356**: 2144-2148.

[45] Flood-Page P, Swenson C, Faiferman I, Matthews J, Williams M, Brannick L, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. *Am J Respir Crit Care Med* 2007; **176**: 1062-1071.

[46] Cowburn AS, Sladek K, Soja J, Adamek L, Nizankowska E, Szczeklik A, et al. Overexpression of leukotriene C4 synthase in bronchial biopsies from patients with aspirin-intolerant asthma. *J Clin Invest* 1998; **101**: 834-846.

[47] Seymour ML, Rak S, Aberg D, Riise GC, Penrose JF, Kanaoka Y, et al. Leukotriene and prostanoid pathway enzymes in bronchial biopsies of seasonal allergic asthmatics. *Am J Resp Crit Care Med* 2001; **164**: 2051-2056.

[48] Nakagome K, Nagata M. Pathogenesis of airway inflammation in bronchial asthma. *Auris Nasus Larynx* 2011; **38**: 555-563.

[49] Akuthota P, Wang H, Weller PF. Eosinophils as antigen-presenting cells in allergic upper airway disease. *Curr Opin Allergy Clin Immunol* 2010; **10**(1): 14-19.

[50] Van Rijt LS, Vos N, Hijdra D, de Vries VC, Hoogsteden HC, Lambrecht BN. Airway eosinophils accumulate in the mediastinal lymph nodes but lack antigen-presenting potential for naive T cells. *J Immunol* 2003; **171**: 3372-3378.

[51] Padigel UM, Hess JA, Lee JJ, Lok JB, Nolan TJ, Schad GA, et al. Eosinophils act as antigen-presenting cells to induce immunity to Strongyloides stercoralis in mice. *J Infect Dis* 2007; **196**: 1844-1851.

[52] Mawhorter SD, Kazura JW, Boom WH. Human eosinophils as antigen-presenting cells: relative efficiency for superantigen- and antigen-induced $CD4_+$T-cell proliferation. *Immunology* 1994; **81**: 584-591.

[53] Del Pozo V, De Andrés B, Martín E, Cárdaba B, Fernández JC, Gallardo S, et al. Eosinophil as antigen-presenting cell: activation of T cell clones and T cell hybridoma by eosinophils after antigen processing. *Eur J Immunol* 1992; **22**: 1919-1925.

[54] Akuthota P, Spencer LA, Radke AL, Weller PF. MHC class II and CD9 localize to lipid rafts in human eosinophils. *Am J Respir Crit Care Med* 2009; doi: 10.1164/ajrccm.

[55] Dykstra M, Cherukuri A, Sohn HW, Tzeng SJ, Pierce SK. Location is everything: lipid rafts and immune cell signaling. *Annu Rev Immunol* 2003; **21**: 457-481.

[56] Lotfi R, Lotze MT. Eosinophils induce DC maturation, regulating immunity. *J Leukoc Biol* 2008; **83**: 456-460.

[57] Borish L, Culp JA. Asthma: a syndrome composed of heterogeneous diseases. *Ann Allergy Asthma Immunol* 2008; **101**: 1-8.

[58] Pitchford SC. Defining a role for platelets in allergic inflammation. *Biochem Soc Trans* 2007; **35**: 1104-1108.

[59] Moritani C, Ishioka S, Haruta Y, Kambe M, Yamakido M. Activation of platelets in bronchial asthma. *Chest* 1998; **113**: 452-458.

[60] Jawień J, Chłopicki S, Gryglewski RJ. Interactions between human platelets and eosinophils are mediated by selectin-P. *Pol J Pharmacol* 2002; **54**: 157-160.

[61] Ulfman LH, Joosten DP, van Aalst CW, Lammers JW, van de Graaf EA, Koenderman L, et al. Platelets promote eosinophil adhesion of patients with asthma to endothelium under flow conditions. *Am J Respir Cell Mol Biol* 2003; **28**: 512-519.

[62] Tutluoglu B, Gurel CB, Ozdas SB, Musellim B, Erturan S, Anakkaya AN, et al. Platelet function and fibrinolytic activity in patients with bronchial asthma. *Clin Appl Thromb Hemost* 2005; **11**: 77-81.

[63] Benton SA, Kumar N, Lerner J, Wiles A, Foerster M, Teach SJ, et al. Airway platelet activation is associated with airway eosinophilic inflammation in asthma. *J Investig Med* 2010; **58**(8): 987-990.

[64] Pitchford SC, Yano H, Lever R, Riffo-Vasquez Y, Ciferri S, Rose MJ, et al. Platelets are essential for leukocyte recruitment in allergic inflammation. *J Allergy Clin Immunol* 2013; **112**(1): 109-118.

[65] Gill MA. The role of dendritic cells in asthma. *J Allergy Clin Immunol* 2012; **129**(4): 889-901.

[66] Dua B, Watson RM, Gauvreau GM, O'Byrne PM. Myeloid and plasmacytoid dendritic cells in induced sputum after allergen inhalation in subjects with asthma. *J Allergy Clin Immunol* 2010; **126**: 133-139.

[67] Chand HS, Schuyler M, Joste N, Hensler C, Tesfaigzi Y, Masten

B, et al. Anti-IgE therapy results in decreased myeloid dendritic cells in asthmatic airways. *J Allergy Clin Immunol* 2010; **125**: 1157-1158.

[68] Broide DH, Finkelman F, Bochner BS, Rothenberg ME. Advances in mechanisms of asthma, allergy, and immunology in 2010. *J Allergy Clin Immunol* 2010; **127**(3): 689-695.

[69] Charbonnier AS, Hammad H, Gosset P, Stewart GA, Alkan S, Tonnel AB, et al. Der p 1-pulsed myeloid and plasmacytoid dendritic cells from house dust mite-sensitized allergic patients dysregulate the T cell response. *J Leukoc Biol* 2003; **73**: 91-99.

[70] Cheng X, Wang C, Qian G, Zhu B. CD80, but not CD86 were up-regulated on the spleen-derived dendritic cells from OVA-sensitized and challenged BALB/c mice. *Immunol Lett* 2003; **89**: 31-38.

[71] Balmelli C, Demotz S, Acha-Orbea H, De Grandi P, Nardelli-Haefliger D. Trachea, lung, and tracheobronchial lymph nodes are the major sites where antigen-presenting cells are detected after nasal vaccination of mice with human papillomavirus type 16 virus-like particles. *J Virol* 2002; **76**: 12596-12602.

[72] Banchereau J, Steinman RM. Dendritic cells and the control of immunity. *Nature* 1998; **392**: 245-252.

[73] Dhodapkar MV, Steinman RM, Krasovsky J, Munz C, Bhardwaj N. Antigen-specific inhibition of effector T cell function in humans after injection of immature dendritic cells. *J Exp Med* 2001; **193**: 233-238.

[74] Hammad H, Charbonnier AS, Duez C, Jacquet A, Stewart GA, Tonnel AB, et al. Th2 polarization by Der p 1-pulsed monocyte-derived dendritic cells is due to the allergic status of the donors. *Blood* 2001; **98**: 1135-1141.

[75] Nadel JA, Busse WW. Asthma. *Am J Respir Crit Care Med* 1998; **157**: 130-138.

[76] Oriss TB, Ostroukhova M, Seguin-Devaux C, Dixon-McCarthy B, Stolz DB, Watkins SC, et al. Dynamics of dendritic cell phenotype and interactions with CD4+T cells in airway inflammation and tolerance. *J Immunol* 2005; **174**: 854-863.

[77] Köhl J, Baelder R, Lewkowich IP, Pandey MK, Hawlisch H, Wang L, et al. A regulatory role for the C5a anaphylatoxin in type 2 immunity in asthma. *J Clin Invest* 2006; **116**: 783-796.

[78] Ito T, Yang M, Wang YH, Lande R, Gregorio J, Perng OA, et al. Plasmacytoid dendritic cells prime IL-10- producing T regulatory cells by inducible costimulator ligand. *J Exp Med* 2007; **204**: 105-115.

[79] Idzko M, Hammad H, van Nimwegen M, Kool M, Willart MA, Muskens F, et al. Extracellular ATP triggers and maintains asthmatic airway inflammation by activating dendritic cells. *Nat Med* 2007; **13**: 913-919.

[80] Kool M, Lambrecht BN. Dendritic cells in asthma and COPD: opportunities for drug development. *Curr Opin Immunol* 2007; **19**: 701-710.

[81] Akbari O, DeKruyff RH, Umetsu DT. Pulmonary dendritic cells producing IL-10 mediate tolerance induced by respiratory exposure to antigen. *Nat Immunol* 2001; **2**: 725-731.

[82] Akbari O, Freeman GJ, Meyer EH, Greenfield EA, Chang TT, Sharpe AH, et al. Antigen-specific regulatory T cells develop via the ICOS-ICOS-ligand pathway and inhibit allergen-induced airway hyperreactivity. *Nat Med* 2002; **8**: 1024-1032.

[83] Allakhverdi Z, Comeau MR, Jessup HK, Yoon BR, Brewer A, Chartier S, et al. Thymic stromal lymphopoietin is released by human epithelial cells in response to microbes, trauma, or inflammation and potently activates mast cells. *J Exp Med* 2007; **204**: 253-258.

[84] Barrett NA, Maekawa A, Rahman OM, Austen KF, Kanaoka Y. Dectin-2 recognition of house dust mite triggers cysteinyl leukotriene generation by dendritic cells. *J Immunol* 2009; **182**: 1119-1128.

[85] Beaty SR, Rose CE, Sung SS. Diverse and potent chemokine production by lung dendritic cells in homeostasis and in allergic lung inflammation. *J Immunol* 2007; **178**: 1882-1895.

[86] Bleck B, Tse DB, Jaspers I, Curotto de Lafaille MA, Reibman J. Diesel exhaust particle-exposed human bronchial epithelial cells induce dendritic cell maturation. *J Immunol* 2006; **176**: 7431-7437.

[87] Lambrecht BN, Hammad H. Biology of lung dendritic cells at the origin of asthma. *Immunity* 2009; **31**(3): 412-424.

[88] Van Rijt LS, Lambrecht BN. Dendritic cells in asthma: a target for novel therapeutics? *Drug Discov Today Ther Strateg* 2006; **3**(3): 299-307.

[89] Barnes PJ. New aspects of asthma. *J Intern Med* 1992; **231**: 453-461.

[90] Silberstein DS. Eosinophil function in health and disease. *Crit Rev Oncol Hematol* 1995; **19**: 47-77.

[91] Discombe G. Criteria of eosinophilia. *Lancet* 1946; **1**: 195-196.

[92] Bochner BS, Undem BJ, Lichtenstein LM. Immunological aspects of allergic asthma. *Annu Rev Immunol* 1994; **12**: 295-335.

[93] Hansel TT, De Vries IJ, Carballido JM, Braun RK, Carballido-Perrig N, Rihs S, et al. Induction and function of eosinophil intercellular adhesion molecule-1 and HLA-DR. *J Immunol* 1992; **149**: 2130-2136.

[94] Pitchford SC. Novel uses for anti-platelet agents as anti-inflammatory drugs. *Br J Pharmacol* 2007; **152**: 987-1002.

[95] Kornerup KN, Page CP. The role of platelets in the pathophysiology of asthma. *Platelets* 2007; **18**(5): 319-328.

[96] Oberle D, von Mutius E, von Kries R. Childhood asthma and continuous exposure to cats since the first year of life with cats allowed in the child's bedroom. *Allergy* 2003; **58**: 1033-1036.

[97] Oldfield WL, Kay AB, Larché M. Allergen-derived T cell peptide-induced late asthmatic reactions precede the induction of antigen-specific hyporesponsiveness in atopic allergic asthmatic subjects. *J Immunol* 2001; **167**: 1734-1739.

[98] Vermaelen KY, Carro-Muino I, Lambrecht BN, Pauwels RA. Specific migratory dendritic cells rapidly transport antigen from the airways to the thoracic lymph nodes. *J Exp Med* 2001; **193**: 51-60.

[99] Grunig G, Banz A, Malefyt RW. Molecular regulation of Th2 immunity by dendritic cells. *Pharmacol Ther* 2005; **106**: 75-96.

[100]Niu N, LeGoff MK, Li F, Rahman M, Homer RJ, Cohn L. Anovel pathway that regulates inflammatory disease in the respiratory tract. *J Immunol* 2007; **178**: 3846-3855.